

Application Ser. No.: 10/031,764

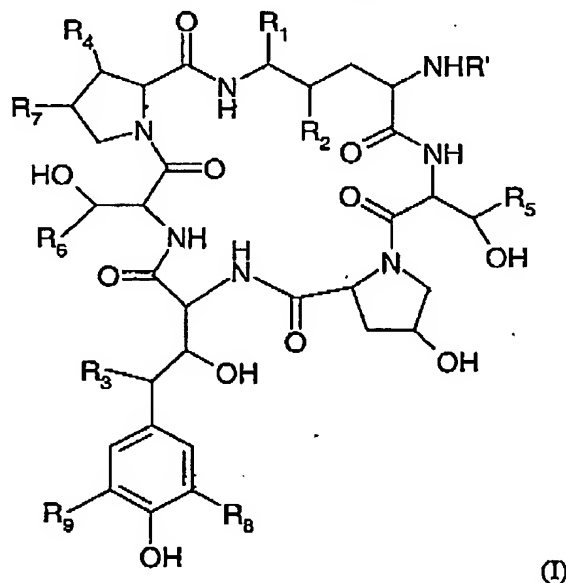
Filing Date: September 30, 2002

Examiner: Audet, Maury A.

Amendment Pursuant to 37 C.F.R. § 1.121IN THE CLAIMS:

The claims set forth below with amendments as indicated will replace all prior versions and listing of claims in the application.

1. (currently amended) A compound selected from the group consisting of a cyclohexapeptide compound of the formula (I)



wherein,

R' is selected from the group consisting of ~~C₁-C₂₀ alkyl~~, C₉-C₂₀ alkyl; C₉-C₂₀ alkenyl; C₉-C₂₀ alkoxyphenyl, phenyl, biphenyl, terphenyl, and naphthyl; C₁-C₁₂ alkylphenyl, C₈-C₁₂ alkenylphenyl, C₁-C₁₂ alkoxyphenyl; linoleoyl; palmitoyl; 12-methylmyristoyl; 10,12-dimethylmyristoyl; and COC₆H₄(p)OC₈H₁₇,

~~R₁ and R₂ are independently~~ is selected from the group consisting of -OH; -CN; -CH₂NH₂; -N₃; aryl; substituted aryl; ~~heterocyclyl and substituted heterocyclic~~ with 1-3 of heteroatoms; ~~aminoalkylamino; mono or di-substituted linear or cyclic~~

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~~aminoalkylamino; imidazolyl; morpholinoethylamino; -OR, wherein R is C₁-C₁₂ alkyl; substituted alkyl of (CH₂)_n-X, where n is 1-5 and X is selected from the group consisting of OH, aryl, Cl, Br, I, COOY, and CN, NH₂ and heterocyclic, wherein Y is selected from the group consisting of C₁-C₆ alkyl, C₂-C₁₂ alkenyl, aryl, fused aryl, substituted aryl, a heterocyclic containing 1-3 heteroatoms, mono or di-substituted aminoalkyl, and a hydroxy protecting group; and R₃ may additionally be imidazolyl;~~

R₃ is selected from the group consisting of -OH; -CN; -CH₂NH₂; -N₃; aryl; substituted aryl; heterocyclyl and substituted heterocyclyl with 1-3 of heteroatoms; aminoalkylamino; mono or di-substituted linear or cyclic aminoalkylamino; imidazolyl; -OR, wherein R is C₁-C₁₂ alkyl; substituted alkyl of (CH₂)_n-X, where n is 1-5 and X is selected from the group consisting of OH, aryl, Cl, Br, I, COOY, CN, NH₂ and heterocyclic, wherein Y is selected from the group consisting of C₁-C₆ alkyl, C₂-C₁₂ alkenyl, aryl, fused aryl, substituted aryl, a heterocyclic containing 1-3 heteroatoms, mono or di-substituted aminoalkyl, and a hydroxy protecting group;

R₂ and R₄ are independently -H or -OH;

R₅ is -H or -CH₃;

R₆ is selected from the group consisting of -H, -CH₃ and -CH₂CONH₂;

R₇ is selected from the group consisting of -H, -CH₃ and -OH;

R₈ and R₉ are independently -H or -CH₂-Sec.amine in which the sec.amine is attached to -CH₂ through its N linkage;
and its non-toxic pharmaceutically acceptable salts.

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2. (currently amended) ~~A~~ The compound of claim 1 wherein R_1 is $-\text{OH}$ or OR , and R_3 is selected from the group consisting of $-\text{OH}$, $-\text{OR}$ and imidazolyl wherein R in each case is selected from the group consisting of $\text{C}_1\text{-C}_{12}$ alkyl, substituted alkyl of $-(\text{CH}_2)_n\text{-X}$, where n is 1-5, X is selected from the group consisting of OH , aryl, Cl, Br, I, COOY , and CN , NH_2 and a heterocyclic, and wherein Y is selected from the group consisting of $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_{12}$ -alkenyl, aryl, fused aryl, substituted aryl, a heteroaryl containing 1-3 heteroatoms, a heterocyclic containing 1-3 heteroatoms, ~~a heterocyclic containing 1-3 heteroatoms,~~ mono or di-substituted aminoalkyl, and a hydroxy protecting group.
3. (currently amended) ~~A~~ The compound of claim 1 wherein R' is selected from the group consisting of linoleoyl, palmitoyl, 12-methylmyristoyl, 10,12-dimethylmyristoyl and $-\text{COC}_6\text{H}_4(p)\text{OC}_8\text{H}_{17}$.
4. (currently amended) ~~A~~ The compound of claim 1 wherein 1) to the nitrogen atom of the secondary amine are attached at least one member of the group consisting of $\text{C}_1\text{-C}_{12}$ alkyl, $\text{C}_2\text{-C}_{12}$ alkenyl, aryl, substituted aryl, alkylaryl and substituted alkylaryl, or 2) or the nitrogen atom of the secondary amine is part of a heterocyclic group, optionally substituted by at least one member of the group consisting of $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ alkenyl, aryl, amino, nitro, and halogen, or 3) the nitrogen atom of the secondary amine is part of a fused heterocyclic group, whereby wherein the heterocyclic group contains 1-3 heteroatoms.
5. (currently amended) ~~A~~ The compound of claim 1 wherein the secondary amine is selected from the group consisting of piperidine, pyrrolidine, 4-methylpiperidine, morpholine, dimethylamine, diisopropylamine, 4-piperidino-piperidine, piperazine, 1-methylpiperazine, 1-(2-fluorophenyl)piperazine, 1-(2-chlorophenyl)piperazine, 1-(2-pyrimidyl)piperazine, 1-(4-fluorophenyl)piperazine, $\text{N}-(\alpha,\alpha,\alpha\text{-trifluoro-m-tolyl})$ piperazine, 1-phenylpiperazine, 1-benzylpiperazine,

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1-(2-pyridyl)piperazine, 1-(4-pyridyl)piperazine, 1-(4-methylphenyl)piperazine, 1-(2,6-dimethylphenyl)piperazine, 1-(1-phenylethyl)piperazine, dibenzylamine, N-(tertbutyl)benzylamine and N-(isopropyl)-benzylamine.

6. (currently amended) ~~A~~ The compound of claim 1, wherein R' is 12-methylmyristoyl, R₁ and R₂ ~~are independently~~ is selected from the group consisting of ~~-OH, -CN, -CH₂NH₂, -N₃, aryl, substituted aryl, -OCH₂C₆H₄, -OCH₃, -OCH₂OH, morpholinoethylamino and imidazolyl heterocyclyl and substituted heterocyclyl having 1-3 heteroatoms, aminoalkylamino, and mono or di-substituted linear or cyclic aminoalkylamino, R₃ is selected from the group consisting of -OH, -CN, -CH₂NH₂, -N₃, aryl, substituted aryl, heterocyclyl and substituted heterocyclyl having 1-3 heteroatoms, aminoalkylamino, and mono or di-substituted linear or cyclic aminoalkylamino, R₅ and R₇ are both -CH₃, R₆ is -H, and R₈ and R₉ are both -H.~~
7. (original) An antifungal composition comprising a fungicidally effective amount of a compound of claim 1, and a non-toxic pharmaceutically acceptable carrier.
8. cancelled.
9. (currently amended) A process for the production of a compound of claim 1 comprising:
- a) reacting a cyclohexapeptide compound of claim 1, wherein R', R₂, R₄, R₅, R₆ and R₇ are as defined in claim 1, R₁ and R₃ are both -OH, and R₈ and R₉ are -H, with an alcohol in the presence of an acid in an aprotic solvent at a temperature of 0°C to 60°C to obtain the corresponding cyclohexapeptide derivative of claim 1 wherein R', R₂, R₄, R₅, R₆ and R₇ are as defined in claim 1, R₁ and R₃ are independently -OH or -OR wherein at least one of R₁ or R₃ is -OR, R is selected from the group

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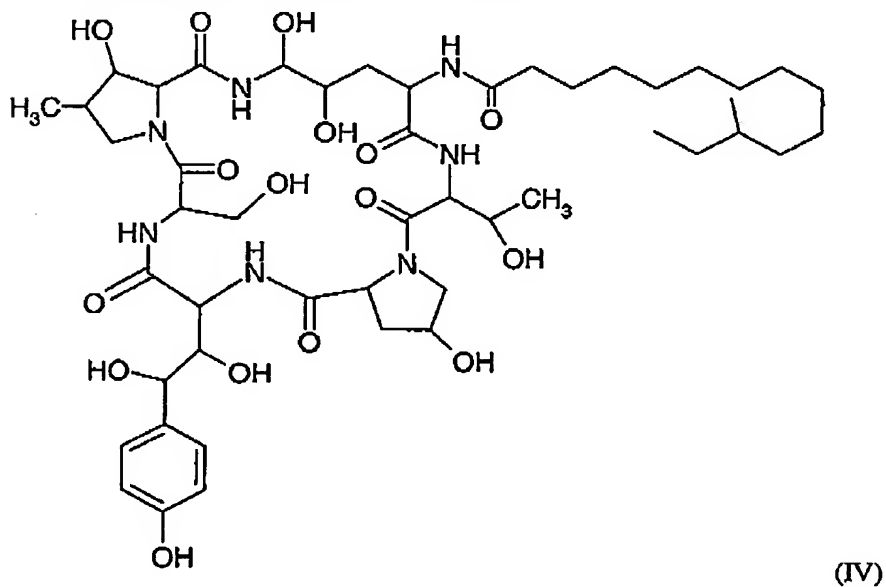
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- consisting of C₁-C₁₂ alkyl, C₂-C₁₂ alkenyl, C₂-C₁₂ alkenyl, fused aryl, substituted aryl, a heterocyclyl containing 1-3 heteroatoms, mono or di-substituted aminoalkyl; and a hydroxy protecting group, and R₈ and R₉ are -H;
- b) reacting the compound of step (a) with a secondary amine in the presence of paraformaldehyde in an aprotic solvent at a temperature of 60°C to 150°C to obtain the desired compound of formula I, isolating and purifying the resulting compound from the reaction mixture in a known manner and optionally converting the compound of formula I into its pharmaceutically acceptable salt in a known manner.

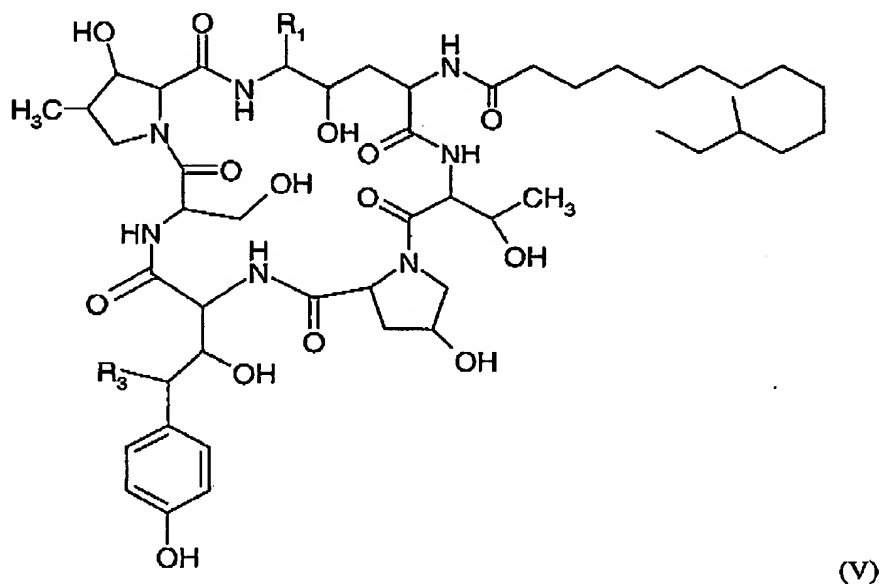
10. (currently amended) A process for the preparation of a cyclohexapeptide compound of claim 1 comprising:

- a) reacting mulundocandin of the formula



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with a nucleophile in the presence of an acid in an aprotic solvent at a temperature of 0°C to 60°C to obtain the corresponding cyclohexapeptide derivative of the formula



wherein R_1 and R_3 are $-OH$ or $-SR$ with at least one of R_1 or R_3 is $-SR$, R is selected from the group consisting of C_1 - C_{12} alkyl, substituted alkyl of $-(CH_2)_n-X$, where n is 1-5, X is Cl, Br, I, $COOY$, CN, NH_2 and a heterocyclic, Y is selected from the group consisting of C_1 - C_6 alkyl; C_2 - C_{12} alkenyl; aryl; fused aryl; substituted aryl; a heterocyclyl containing 1-3 heteroatoms; mono or di-substituted aminoalkyl; and a hydroxy protecting group;

- b) reacting the compound of step (a) with an oxidizing agent in an aqueous medium at a temperature of 20°C to 60°C to obtain the corresponding sulfones of formula V wherein R_1 and R_3 are $-OH$ or $-S(O_2)R$, with at least one of R_1 or R_3 is $-SO_2R$, R is selected from the group consisting of C_1 - C_{12} alkyl, substituted alkyl of $-(CH_2)_n-X$, where n is 1-5, X is Cl, Br, I, $COOY$, CN, NH_2 and a heterocyclic, Y is selected from the group consisting of C_1 - C_6 alkyl; ~~C_1 - C_{12} alkenyl;~~ C_2 - C_{12} alkenyl; aryl; fused aryl;

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- substituted aryl; a heterocyclyl containing 1-3 heteroatoms; mono or di-substituted aminoalkyl; and a hydroxy protecting group;
- c) reacting the sulfone of step(b) with a nucleophile in a solvent at a temperature of 20°C to 60°C to obtain the desired compound of claim 1, isolating and purifying the resulting compound and optionally converting the compound of claim 1 into its pharmaceutically acceptable salt in a known manner.